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REVIEW ARTICLE

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COMET: monitoring mitochondrial shock in anesthesiology and intensive care medicine

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Abstract

Mitochondria, as the cellular end-users of oxygen and responsible for approximately 98% of total body oxygen consumption, play a significant role in the development of organ dysfunction during shock. Therefore, integrating information on mitochondrial oxygen homeostasis with macroscopic observations of macrocirculation and microcirculation is crucial for monitoring critically ill patients or those undergoing high-risk surgery. However, current clinical practice still lack reliable surrogate parameters for assessing mitochondrial function. The Cellular Oxygen METabolism (COMET) monitor, utilizing the protoporphyrin IX triplet state lifetime technique (PpIX-TSLT), represents the first clinical device capable of non-invasive, in vivo measurement of mitochondrial oxygen pressure and oxidative phosphorylation. Recent research suggests that implementing this real-time bedside monitoring will provide additional insights into microcirculatory dynamics and enhance patient management. This review will comprehensively detail the rationale, methodologies, evolution, and clinical applications of the technique, aiming at improving the understanding of mitochondrial pathology in daily clinical practice and facilitating the development of targeted therapeutic strategies.

Keywords COMET, Mitochondrial oxygen metabolism, Non-invasive monitoring at the bedside, PpIX-TSLT

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SHOUT
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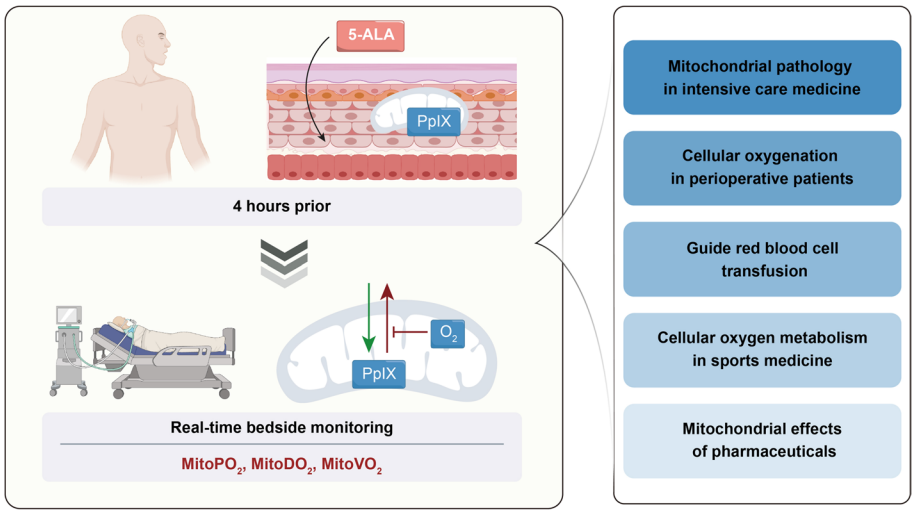
Graphical Abstract



1 Introduction

Optimizing macrocirculatory and microcirculatory function, as well as ensuring sufficient tissue oxygen delivery, are crucial for maintaining cellular oxygenation and organ function in perioperative and intensive care patients. Management strategies to achieve adequate cellular oxygenation primarily involve administering fluids, blood transfusion, and vasoactive medication, with a focus on normalizing systemic circulatory parameters such as mean arterial blood pressure, cardiac output, hemoglobin levels, lactate levels, and peripheral and central venous oxygen saturation [1]. However, these traditional surrogate parameters offer limited prognostic value [2], as the definition of adequate cellular oxygenation remains elusive.

Mitochondria, as the cellular end-users of oxygen and responsible for approximately 98% of total body oxygen consumption, play a significant role in the development of organ dysfunction during shock. Oxygen is ultimately utilized at complex IV of the electron transport chain in the inner mitochondrial membrane. In critical illness, the interplay between aerobic and anaerobic metabolism becomes crucial, as disruptions in the balance between oxygen supply and demand are common. In the case of mitochondrial dysfunction, such as after sepsis, cyanide poisoning, or carbon monoxide intoxication that directly inhibit components of the electron transport chain, optimizing macrocirculation and microcirculation alone is not likely to improve aerobic cell metabolism [3]. Clinicians, however, still lack reliable surrogate parameters of mitochondrial function.

Various perioperative factors, including anesthetic agent and inflammatory responses following surgical manipulation, can significantly impact mitochondrial function in vital organs [4–6]. The inflammatory reactions from trauma contribute to increased vascular permeability, resulting in fluid efflux from the intravascular space into the interstitial region, followed by microcirculatory dysfunction and increased distance from blood circulation to target cell mitochondria. The brain's high metabolic activity renders it particularly vulnerable to periods of low mean arterial blood pressure and hypoxia. Our animal study has highlighted the critical role of neural mitochondrial function in the development of postoperative neurocognitive dysfunction [7]. Additionally, investigations in elderly patients have identified the preoperative platelet Bioenergetic Health Index, a comprehensive metric integrating various indicators of mitochondrial function into a single value, potentially serving as a reliable indicator of the brain's susceptibility to postoperative delirium [8].

However, while ex vivo techniques such as Seahorse XF technology or Oroboros O2k system provide detailed insights into mitochondrial respiratory chain function, measurements in isolated cell, mitochondrial suspensions, or tissue biopsy homogenates may not fully represent the in vivo environment. This is due to evaluating mitochondrial function under physiological or pathophysiological conditions is crucial for understanding changes in oxidative phosphorylation [9]. Moreover, mitochondrial function are typically assessed by laboratory tests on live cells following invasive measures on

patients, such as blood withdrawal or muscle biopsy [10]. Ethical and technical challenges limit access to vital human biopsy tissue, particularly for repeated sampling to monitor disease progression. These all underscore the necessity of developing non-invasive, real-time monitoring system for mitochondrial performance at the bedside.

We are about to initiate a clinical study to investigate the role of mitochondrial function in the development of postoperative neurocognitive dysfunction. Therefore, we reviewed current in vivo mitochondrial respirometry techniques, their methodologies, and the underlying pathophysiological principles. The Cellular Oxygen METabolism (COMET) monitor, utilizing the protoporphyrin IX triplet state lifetime technique (PpIX-TSLT), represents the first clinical device capable of non-invasive, in vivo measurement of mitochondrial oxygen tension and oxygen metabolism [11–13]. This review will detail the rationale, methodologies, and evolution of this clinically applicable technique for assessing mitochondrial performance. Additionally, we will summarize its potential applications in perioperative and intensive care medicine, while addressing associated challenges.

2 Methodology of COMET

2.1 Fundamental principles

The pioneering work by E.G. Mik et al. developed PpIX-TSLT technique based on the principle of oxygen-dependent quenching of the excited triplet state of protoporphyrin IX (PpIX) [14]. As the final precursor of heme in the biosynthetic pathway, PpIX is synthesized within mitochondria. Normally found in very low concentrations in human skin, PpIX is undetectable using COMET. Administration of exogenous 5-aminolevulinic acid (5-ALA) significantly increases PpIX concentration. Upon photo-excitation with green light, PpIX emits delayed fluorescence, which is efficiently quenched by molecular oxygen in mitochondria [15].

After validating the ability of PpIX-TSLT to consistently quantify mitochondrial oxygen tension in living cells [16], isolated organs [17], and animal studies [18, 19], a device based on PpIX-TSLT was developed for non-invasive measurement of mitochondrial oxygen metabolism in human skin at the bedside [20]. This device, known as the COMET monitor (Photonics Healthcare B.V., Utrecht, Netherlands), is now commercially available, with a detailed description provided by Ubbink et al. [11]. The system comprises two main components. The first component is the monitor, featuring a multi-touch screen user interface, light source, detection system, and processing units. The second component is the skin sensor, equipped with two optical fibers for emitting green laser light and detecting delayed fluorescence. The monitor directly displays the absolute value of mitochondrial oxygen pressure ($mitoPO_2$) on the screen, offering three measurement types: Single, Interval, and Dynamic. To synthesize a sufficient concentration of PpIX for $mitoPO_2$ measurements, a self-adhesive patch containing 8 mg of 5-ALA is applied to the skin at least 4 h prior. After removal of the 5-ALA patch, the skin sensor is applied to the treated area.

2.2 Oxygen homeostasis at the mitochondrial level

The final destination of oxygen molecules in vivo is the mitochondria, where they are utilized in oxidative phosphorylation. Therefore, mitochondrial oxygen tension, or mitochondrial oxygen pressure, which refers to the concentration of oxygen molecules within the mitochondria, can serve as a direct indicator of cellular-level oxygen balance. Mitochondrial oxygen supply depends on microvascular blood flow, hemoglobin concentration, hemoglobin saturation, local oxygen-hemoglobin dissociation characteristics, and any factor affecting oxygen diffusion from erythrocytes in microcirculation to tissue cells. On the demand side of the oxygen balance, mitochondrial oxidative phosphorylation, which produces adenosine triphosphate (ATP), accounts for the majority of oxygen consumption, with a small fraction attributable to uncoupling via proton leak across the mitochondrial inner membrane [15]. Current techniques appear adequate for monitoring tissue oxygenation in most patients, yet information regarding oxygenation at the endpoint in the oxygen cascade remains insufficient. Therefore, integrating mitochondrial oxygenation and oxygen consumption with macroscopic observations of macrocirculation and microcirculation proves crucial for monitoring critically ill patients or those undergoing high-risk surgery.

2.3 Main variables

Using the PpIX-TSLT technique, $mitoPO_2$ can be determined in vivo and has been validated and calibrated in various organs and tissues such as the liver [16], heart [17], and skin [21]. Theoretically, $mitoPO_2$ should be at the lower end of the oxygen distribution in tissues, as mitochondria are the ultimate destination of oxygen diffusion. However, baseline $mitoPO_2$ measured by the PpIX-TSLT technique appears to closely approximate microvascular oxygen tension [18, 22] and known values of tissue or interstitial oxygen levels [23, 24], depending on the measurement site and the tissue's respiratory rate.

Typically reported baseline cutaneous $mitoPO_2$ values range from around 44 mmHg [20] to 66 mmHg [25], which align well with other measurements in the skin [24]. To ensure that high $mitoPO_2$ values were not due to improper calibration, a direct calibration of the COMET in human skin was conducted [12]. This involved a two-point calibration process: first, blocking oxygen supply

through microvascular occlusion to obtain the minimal mitoPO$_2$ value, and then inhibiting mitochondrial respiration with cyanide cream to achieve values that were comparable to arterial oxygen tension [21]. It is important to note that mitoPO$_2$ represents the average oxygen balance across all mitochondria measured by the COMET sensor. A low mitoPO$_2$ value may indicate that some of these mitochondria are hypoxic.

In addition to mitoPO$_2$ measurements [20], the COMET system also provides insights into mitochondrial function through measurements of mitochondrial oxygen consumption (mitoVO$_2$) [19, 26, 27] and oxygen delivery (mitoDO$_2$) [25]. After recording mitoPO$_2$ for approximately 30 s (one measurement per second), pressure was applied to the skin with the probe for 45 s to temporarily interrupt local microcirculation, resulting in a decrease of mitoPO$_2$. MitoVO$_2$ can then be derived from the resulting oxygen disappearance curve, where the slope represents the oxygen disappearance rate [19, 26, 28]. Once mitoPO$_2$ dropped close to zero or showed no further decline, pressure was maintained for an additional 10 s. Subsequently, the pressure was released to allow for local re-oxygenation, and mitoDO$_2$ is calculated based on the slope of mitoPO$_2$ increase [29].

2.4 Monitoring sites

The skin is considered an ideal target organ for COMET measurements [23]. During sympathetic activation, blood flow shifts away from the skin towards vital organs, making it one of the first organs to become hypoxic during hemodynamically unstable conditions [30]. Thus, changes in cutaneous mitoPO$_2$ levels may reflect alterations in cellular oxygenation of other vital organs [27]. The skin of the sternum is recommended as a measurement site due to its central location, minimizing influences from temperature changes, movement, and peripheral vasoconstriction. MitoPO$_2$ can also be measured on other sites such as the upper arm [31] and the anterior aspect of the thigh [32]. However, for measuring mitoVO$_2$, the arm or thigh is not preferred because the skin at these sites lacks bone support to effectively block microcirculation with slight pressure.

The use of PpIX-TSLT is not limited to skin measurements. A recent study demonstrated its feasibility in assessing mucosal oxygenation in the gastrointestinal system using endoscopy [33]. In healthy volunteers, 5-ALA was orally administered, and oxygen-dependent delayed fluorescence was measured via an optical fiber through the endoscope's accessory channel four hours later. The study identified an optimal oral dose of 5 mg/kg 5-ALA, with the duodenal bulb and descending duodenum recognized as suitable measurement sites.

2.5 The safety of 5-ALA

While PpIX-TSLT is non-invasive and safe for use in humans, potential phototoxicity of PpIX after sunlight exposure must always be considered as a side effect necessitating risk and safety assessment for any intended application [34, 35]. Compared to systemic 5-ALA administration, local application is preferred. The skin needs protection from light during 5-ALA application to prevent PpIX consumption. Following the procedure, it is crucial to limit skin exposure to sunlight in the subsequent days to prevent photosensitization. In a study involving the use of PpIX-TSLT in the gastrointestinal system, phototoxic side effects occurred in the group receiving an oral dose of 20 mg/kg 5-ALA, which resolved within 24 h in the skin but were absent in the gastrointestinal tract [33].

2.6 How COMET differs from other in vivo techniques assessing oxygenation

Oxygen transport from microcirculation into tissue cells occurs primarily through diffusion. Therefore, direct comparison of PpIX-TSLT with other techniques is unreliable due to varying oxygen tensions in different compartments. However, PpIX-TSLT offers distinct advantages: it precisely measures oxygenation at the mitochondrial level within cells, a capability unmatched by current clinical devices at the bedside. Pulse oximetry typically assesses oxygenation at the arteriolar side of the microcirculation, while near-infrared spectroscopy (NIRS) are biased toward the venous compartment [11]. Peripheral oxygen saturation (SpO_2), arterial partial pressure of oxygen (PaO_2), mixed venous oxygen saturation (SvO_2), and tissue oxygen saturation (StO_2) cannot serve as satisfactory substitutes for assessing cellular-level oxygenation.

Tissue oxygen tension (tPO$_2$) monitoring allows continuous assessment of local oxygen supply–demand balance. tPO$_2$ decreases when local oxygen demands exceed supply. Conversely, pathological dysfunction in oxidative phosphorylation can lead to oxygen delivery surpassing consumption, resulting in elevated tPO$_2$ levels. This is illustrated by the higher tPO$_2$ observed in sepsis patients [23]. Furthermore, simultaneous changes in supply and demand may not necessarily affect tPO$_2$. Both laboratory [36] and clinical studies [11, 12] have shown that cutaneous mitoPO$_2$ demonstrates greater sensitivity in detecting subtle changes in local oxygen balance compared to several other tissue oxygenation assessment techniques. Unlike NIRS, where oxygen saturation values are uncalibrated and baseline variations occur, PpIX-TSLT values are calibrated and remain stable after initial calibration without requiring recalibration during use.

Perioperative cerebral hypoxia, considered an independent risk factor for postoperative neurocognitive dysfunction, can be prevented by a NIRS-derived technique known as regional cerebral oxygen saturation ($rScO_2$) [37]. However, most studies have not found a significant association between $rScO_2$ values and postoperative neurocognitive dysfunction [38, 39]. Importantly, no study has yet determined the critical cerebral mitochondrial oxygen tension before or during the onset of postoperative neurocognitive dysfunction, especially in high-risk patients. The PpIX-TSLT technique may offer a non-invasive, real-time monitoring approach to investigate cerebral mitochondrial function in the development of postoperative neurocognitive dysfunction.

2.7 Comparison of COMET with other in vivo techniques for assessing mitochondrial function

Over the past few decades, numerous techniques have been developed to assess the respiratory chain of mitochondria in vivo. The most commonly used methods involve semi-quantitative measurements of mitochondrial nicotinamide adePrpfessor Xiaoping Gu and Professor Zhengliang Ma are members of the Editorial Board in Anesthesiology and Perioperativenine dinucleotide (NADH), flavin adenine dinucleotide, or the oxidation state of cytochrome c oxidase (oxCCO). However, standard clinical monitoring of mitochondrial metabolic states using NADH fluoroscopy remains impractical due to its sensitivity to factors such as hemoglobin levels, which can cause artifacts [40]. Similarly, measuring oxCCO using broadband near-infrared spectroscopy faces challenges in data interpretation due to tissue-specific effects influencing the signal recovery [41].

Another widely used method is Nuclear Magnetic Resonance (NMR) spectroscopy, which assesses mitochondrial ATP production by measuring changes in phosphometabolites [42]. However, a limitation of NMR spectroscopy is its reliance on a magnetic resonance imaging scan, which makes it costly and unsuitable for real-time bedside monitoring.

3 Clinical application

The first prototype of a clinical PpIX-TSLT monitor designed for human skin was described in 2015 [27]. Its feasibility and safety were further established in healthy volunteers [11, 20], paving the way for clinical studies focused on monitoring mitochondrial oxygenation and oxygen metabolism in perioperative and intensive care medicine [28, 43]. The current research findings represent a significant advancement in this field.

3.1 Measuring exercise-induced changes in mitochondrial oxygen metabolism

In a study examining the effects of exercise on COMET variables in healthy individuals, physical activity significantly decreased $mitoVO_2$. However, $mitoPO_2$ and $mitoDO_2$ remained unchanged compared to their levels before physical activity, although $mitoPO_2$ exhibited a significant increase during ergometry [25]. Another study examined changes in COMET variables during cardiopulmonary exercise testing (CPET) and their correlation with gas exchange and capillary blood gas analyses [44]. $MitoPO_2$ and $mitoDO_2$ exhibited notable differences across the three phases of CPET: aerobic metabolism, aerobic-anaerobic transition, and anaerobic metabolism. There was a marked increase in $mitoPO_2$ from aerobic to aerobic-anaerobic phases, followed by a significant decrease in the anaerobic phase, defining the peak mitochondrial threshold. Conversely, $mitoVO_2$ showed no significant differences among the phases. The study highlighted varying associations between COMET and CPET variables throughout the phases. During aerobic and aerobic-anaerobic phases, $mitoPO_2$ positively correlated with CPET variables that increased across phases, whereas these relationships reversed during the anaerobic phase. Additionally, the study found that capillary partial pressure of carbon dioxide ($PcCO_2$) and end-tidal carbon dioxide ($PETCO_2$) were positively associated with $mitoPO_2$, whereas capillary partial pressure of oxygen (PcO_2) and end-tidal oxygen ($PETO_2$) showed a negative association. These findings underscore the importance of understanding interactions across different levels (from organs to cells to cellular organelles) in critical care and sports medicine contexts.

3.2 Feasibility Exploration as a transfusion trigger

Numerous factors influence tissue oxygenation, yet current clinical practice relies solely on hemoglobin levels to guide red blood cell transfusions. $MitoPO_2$ directly reflects the cellular oxygen balance between supply and demand [15]. Therefore, measuring $mitoPO_2$ may theoretically provide crucial information about the presence of cellular hypoxia and an individual's need for transfusion [45].

This presupposition was first demonstrated in pigs undergoing hemodilution [36]. The reduction in cutaneous $mitoPO_2$ occurred at least one hemodilution step prior to changes in hemodynamic parameters and lactate levels. The sudden drop in cutaneous $mitoPO_2$, coupled with the non-response of StO_2 in skeletal muscle at the physiological limit of an individual pig, suggests that $mitoPO_2$ could serve as a potential trigger for individual blood transfusion. Additionally, Harms et al. presented a case that underscores the potential of $mitoPO_2$ as a supplementary monitoring parameter for perioperative transfusion management [43]. A notable observation from this case report is that, despite the maintenance of hemodynamic parameters through the administration of vasoactive agents and fluid resuscitation during

continuous blood loss, mitoPO$_2$ and microcirculatory parameters showed a distinct decline, indicating cellular distress. This condition was reversed through the transfusion of red blood cells.

In a recently published pilot study involving patients with chronic anemia, varying mitoPO$_2$ responses to red blood cell transfusion and fluid administration were observed [46]. The decrease in cutaneous mitoPO$_2$ observed after red blood cell transfusion, though still requiring further clarification, may be related to the specific physiological alterations caused by chronic anemia. Nonetheless, these findings highlight the significance of monitoring mitoPO$_2$ in optimizing transfusion practices in the fields of anesthesiology and critical care.

3.3 Early Exploration in perioperative patients

Safeguarding adequate organ perfusion and tissue oxygenation is a crucial responsibility of anesthesiologist during the perioperative period, traditionally relying on standard parameters such as blood pressure, SpO$_2$, PETCO$_2$, urine output, and lactate levels. Since the introduction of the COMET system into clinical practice, several studies have explored mitochondrial oxygenation in surgical patients. This non-invasive bedside monitoring tool enables anesthesiologist to adjust their management based on real-time cellular oxygenation.

The first description of the COMET system published in 2017 showed an incidental finding during neurosurgery [11]. To treat persistent intraoperative hypertension, a patient received an intravenous bolus of clonidine, which initially caused peripheral vasoconstriction due to its direct α1-agonist effect. This resulted in a decrease of cutaneous mitoPO$_2$ from a stable level of 48 to 16 mmHg, accompanied by reductions in microvascular flow and velocity parameters. However, no concurrent changes were observed in StO$_2$.

Subsequently, another clinical study firstly validated the feasibility and safety of intraoperative use of the COMET system in neonates [32]. This study focused on newborns undergoing surgical repair for congenital diaphragmatic hernia or esophageal atresia, prompted by the current technical limitations of cardiovascular monitoring in neonates and the documented high risk of postoperative brain injury in children with these congenital anomalies [47, 48]. Their findings confirmed that pathophysiological disturbances resulted in perturbations in mitoPO$_2$, highlighting that COMET monitoring could detect mitochondrial hypoxia not observable with standard monitoring modalities, including rScO$_2$.

The same phenomenon was observed in another pilot study [31], which successfully demonstrated the feasibility of measuring cutaneous mitoPO$_2$ using the COMET system during cardiothoracic surgery. Prolonged cardiopulmonary bypass (CPB) run times were noted to adversely affect microcirculation [49] and were associated with poor outcomes [50]. The study revealed a progressive decrease in cutaneous mitoPO$_2$ with increasing CPB duration, whereas simultaneous StO$_2$ decreased only during extreme intraoperative events such as deep hypothermia with circulatory arrest. MitoPO$_2$ also notably decreased during aortic cross-clamping and increased upon clamp release, whereas StO$_2$ did not, indicating that cutaneous mitoPO$_2$ may respond earlier or more sensitively to hemodynamic and microcirculatory changes compared to StO$_2$. Additionally, the study identified an association between the duration of mitoPO$_2$ below 20 mmHg and the risk of developing acute kidney injury, likely due to poor skin perfusion preceding perfusion deficits in other organs. These findings underscore the potential of cutaneous mitoPO$_2$ measurements in assessing cumulative oxygen deprivation, thereby aiding in the preservation of organ function during cardiothoracic surgery.

Furthermore, the COMET system is currently being utilized in a prospective cohort study focusing on obese patients undergoing laparoscopic sleeve gastrectomy. This study aims to assess the longitudinal changes in mitochondrial oxygen metabolism, along with variations in patients' body composition, metabolomic, and immunological factors, both before and after surgery. Through this comprehensive approach, researchers seek to unravel the mechanisms underlying the therapeutic benefits of bariatric surgery [51].

A recent observational study demonstrated the feasibility of utilizing the COMET system during neurosurgical procedures, revealing that mitoPO$_2$ remains stable and predictable under stable hemodynamic conditions [52]. To exclude the influences of anesthesia induction and oxygen therapy with mechanical ventilation, measurements were conducted continuously from the beginning to the end of surgery. Researchers found the mitoPO$_2$ value tended to decrease over time. An increase in temperature gives a drop in mitoPO$_2$ whilst the cutaneous microvascular blood flow and StO$_2$ remained stable. Interestingly, baseline mitoPO$_2$ levels (60 ± 17 mmHg) observed were higher compared to previously reported values in healthy volunteers (44 ± 17 mmHg) [20]. This discrepancy may be attributed to the higher inspiratory oxygen fraction administered during surgery or reduced mitochondrial metabolism during general anesthesia. Further clinical research is needed to elucidate the potential benefits of monitoring mitochondrial oxygenation during the perioperative period.

3.4 Applications in intensive care medicine

Maintaining oxygen homeostasis, which involves achieving a stable balance of oxygenation and oxygen metabolism

within a normal range, is crucial in the treatment of critically ill patients. PpIX-TSLT technology offers the capability to distinguish disturbances in oxygen homeostasis at the cellular level during critical illness. For instance, elevated blood lactate levels in sepsis can be caused by tissue hypoxia, mitochondrial dysfunction, or impaired liver clearance. Integrating bedside mitochondrial function measurements could provide valuable insights and potentially facilitate the development of innovative treatment strategies for critically ill patients. The COMET system has already been utilized in several studies involving critically ill patients [53, 54].

Inadequate tissue oxygenation is a critical issue in various forms of shock, including sepsis, where mitochondrial dysfunction is considered a key contributor to multiorgan failure [3, 55, 56]. The dysfunction manifests as disturbances in oxidative phosphorylation, structural damage, and oxidative stress [57]. This may explain why early goal-directed therapy focusing on hemodynamic parameters and tissue oxygenation does not consistently improve outcomes [58]. In two preclinical studies using the PpIX-TSLT technique, reduced mitoVO$_2$ was observed in the skin of rats treated with lipopolysaccharide[26, 27]. Subsequent clinical studies in patients during the acute phase of sepsis further validated the feasibility of this non-invasive bedside monitoring in patients with sepsis [54]. To address potential confounding effects of excessive edema on COMET measurements, researchers evaluated patients' hydration status using bioimpedance analysis and found that higher hydration levels correlated with lower mitoPO$_2$ and mitoVO$_2$ levels. Additionally, patient sex emerged as a covariate in COMET variables, with lower values observed in males. Conversely, neither ventilation status nor catecholamine dosage showed significant associations with COMET variables.

One more point to be noted is the conflicting literature on mitochondrial function in sepsis [59], with reports of both unchanged [60] and even improved mitochondrial function [61]. These discrepancies can be attributed to variations in sepsis models, different phases of the condition, diverse target organs and methodologies, as well as experimental limitations due to ex vivo measurements [62]. Therefore, adopting a standardized monitoring pattern with PpIX-TSLT in sepsis is anticipated to enhance understanding of its pathogenesis and facilitate the development of improved therapeutic strategies aimed at restoring aerobic metabolism and cellular function.

Patients with cardiovascular disease represent another cohort showing reduced mitochondrial oxygen metabolism [63]. Oxygen deficiency at the level of cardiomyocyte mitochondria is hypothesized as an important contributor to the onset of cardiac failure [64]. The application of in vivo mitochondrial oxygenation measurement within the working heart provides a crucial parameter for monitoring underling physiological changes. In a study involving rats with induced right ventricular failure due to pulmonary arterial hypertension, the PpIX-TSLT technique did not reveal decreased mitochondrial oxygenation [65]. In this study, rats received 200 mg/kg 5-ALA via intraperitoneal injection, and a fiber optic probe was positioned transdiaphragmally approximately 1 mm from the right ventricle of the beating heart at 2 h after 5-ALA injection. The mitoPO$_2$ values within the right ventricle were either higher (under baseline conditions) or equal (under reduced oxygen supply or increased workload conditions) to those of healthy hearts, suggesting decreased mitochondrial oxygen consumption rather than hypoxia during the transition from compensated hypertrophy to cardiac failure.

Mitochondrial dysfunction has also been linked to the pathophysiology of COVID-19 [66]. An observational pilot study compared in vivo and ex vivo mitochondrial function in COVID-19 patients [67]. The median mitoVO$_2$ value in the skin of these patients, measured both on the day of admission to the intensive care unit and seven days after, was similar and tended to be slightly lower (though not significantly) compared to age- and gender- matched healthy volunteers. In terms of ex vivo mitochondrial respiration measurements, there was no substantial difference in basal platelet respiration among the groups. However, the basal respiration of peripheral blood mononuclear cells (PBMC) was approximately 80% higher in COVID-19 patients on the day of intensive care unit admission compared to healthy controls. Given that PBMC metabolic changes may be associated with their involvement in the inflammatory response, peripheral platelets might serve as a better indicator of the systemic bioenergetic state. Additionally, the study found that mitoVO$_2$ in patients without COVID-19 undergoing general anesthesia, which was measured after anesthesia induction and before the start of cardiothoracic surgery, was the lowest among all observed groups.

These studies conducted preliminary explorations to assess the feasibility of PpIX-TSLT measurements using the COMET system in critically ill patients. Among the main variables provided by the COMET system, mitoVO$_2$, which reflects mitochondrial oxygen consumption, may be related to parameters derived from Seahorse or Oroboros. More studies comparing in vivo and ex vivo techniques for measuring mitochondrial function in critically ill patients are urgently needed. The results of the present studies substantiate the hypothesis that cutaneous COMET parameters reflect the comprehensive outcome of cellular oxygen metabolism, in which all the factors can potentially affect the mitochondrial metabolism in vital organs during critical illness. Future studies

in larger cohorts of critically ill patients across various disease stages would be of great diagnostic and therapeutic value.

3.5 Testing mitochondrial effects of pharmaceuticals

Mitochondria are emerging as an increasingly significant therapeutic target for various disease, including neurodegenerative [68], metabolic [69], and cardiovascular conditions [63]. Progress in diagnosis and treatment of mitochondrial dysfunction might greatly benefit from the non-invasive PpIX-TSLT technique for assessing mitochondrial function in vivo. A pharmacological model of mitochondrial dysfunction induced by simvastatin has been validated in healthy subjects using the COMET system [29]. After 4 weeks of simvastatin administration, the mean mitoVO$_2$ measured in the skin using PpIX-TSLT showed an increase of 13%, while the oxygen consumption rate in muscle tissue determined by NIRS showed an increase of 13.50%.

3.6 Limitations

The requirement for 5-ALA to enhance mitochondrial PpIX levels is a notable disadvantage of PpIX-TSLT in its current application. Despite 5-ALA's ability to penetrate the stratum corneum into the dermis, the heme-synthesis pathway is inactive in most dermis cells, limiting PpIX synthesis primarily to the epidermis after topical administration of 5-ALA on healthy skin [70]. Consequently, the signal origin of the COMET is restricted to the epidermis, with a thickness of approximately 0.1 mm [71]. Despite the good stability and sensitivity of the PpIX-TSLT technique, it is recommended to perform multiple concurrent monitoring to enhance the reliability of results.

Additionally, while systemic administration of 5-ALA is clinically employed in photodynamic diagnosis and therapy of cancer [72], and its use in neurosurgery [73–75] suggests technical feasibility for exploring the link between intraoperative regional cerebral mitoPO$_2$ values and the occurrence of postoperative neurocognitive disorders, the distinct metabolism of normal cells versus tumor cells and the current inability to localize systemic 5-ALA administration to neurons pose significant technical challenges for studying mitochondrial oxygen metabolism in neurons during the onset of postoperative neurocognitive dysfunction.

4 Conclusion and prospect

Maintaining adequate tissue oxygenation remains one of the most crucial tasks for anesthesiologists and intensive care physicians, yet our understanding of in vivo mitochondrial oxygen tension and metabolism is currently limited. The COMET monitor offers new insight into mitochondrial oxygen homeostasis at the bedside. MitoPO$_2$ reflects the cellular balance between oxygen supply and consumption, while mitoDO$_2$ indicates local oxygen delivery and may serve as a surrogate parameter for microcirculatory function. MitoVO$_2$ measures mitochondrial oxygen consumption, reflecting aerobic respiratory function. Current studies demonstrate the feasibility of in vivo measurement of these mitochondrial parameters using the COMET monitor. Moreover, research indicates that cutaneous mitochondrial parameters are more sensitive compared to tissue oxygen saturation and systemic markers of cellular hypoxia, such as lactate. This emphasizes the necessity for further research to explore how changes in cutaneous mitochondrial parameters can predict mitochondrial performances of other vital organs in critically ill and perioperative patients.

Abbreviations

5-ALA	5-Aminolevulinic acid
ATP	Adenosine triphosphate
CPB	Cardiopulmonary bypass
CPET	Cardiopulmonary exercise testing
COMET	Cellular Oxygen METabolism
MitoDO$_2$	Mitochondrial oxygen delivery
MitoPO$_2$	Mitochondrial oxygen pressure
MitoVO$_2$	Mitochondrial oxygen consumption
NADH	Nicotinamide adenine dinucleotide
NIRS	Near-infrared spectroscopy
NMR	Nuclear Magnetic Resonance
oxCCO	Oxidation state of cytochrome c oxidase
PaO$_2$	Arterial partial pressure of oxygen
PBMC	Peripheral blood mononuclear cells
PcCO$_2$	Capillary partial pressure of carbon dioxide
PcO$_2$	Capillary partial pressure of oxygen
PETCO$_2$	End-tidal carbon dioxide
PETO$_2$	End-tidal oxygen
PpIX	Protoporphyrin IX
PpIX-TSLT	Protoporphyrin IX triplet state lifetime technique
rScO$_2$	Regional cerebral oxygen saturation
SpO$_2$	Peripheral oxygen saturation
StO$_2$	Tissue oxygen saturation
SvO$_2$	Mixed venous oxygen saturation
tPO$_2$	Tissue oxygen tension

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Authors' contributions

XPG, ZLM and YY proposed the idea and designed the framework of the manuscript. YY drafted the manuscript. ZW revised the manuscript and edited critically. All the authors contributed to the article and approved the submitted version.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
All authors gave their content for publication.

Competing interests
Professor Xiaoping Gu and Professor Zhengliang Ma are members of the Editorial Board in Anesthesiology and Perioperative Science and recuses themselves from every editorial procedure of this submission including the peer-review and academic decisions. The authors declare no other competing interests.

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